Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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hydrocortisone 5mg and 20mg modified-release tablets (Plenadren®)

SMC No. 848/12

Shire Pharmaceuticals Limited

04 November 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan process

hydrocortisone modified release (Plenadren®) is not recommended for use within NHS Scotland.

Indication under review: Treatment of adrenal insufficiency in adults.

Compared with three times daily immediate-release hydrocortisone, once daily modified-release hydrocortisone (taken in the morning) demonstrated approximately 20% lower cortisol exposure over 24 hours. A high cortisol concentration peak in the morning and gradual decline during the afternoon with modified-release hydrocortisone partially reflects the physiological profile.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adrenal insufficiency (AI) in adults.

Dosing Information

Hydrocortisone modified-release (MR) tablets are taken once daily in the morning and the dose is individualised according to clinical response. A common maintenance dose is 20mg to 30mg daily, although some patients may require a higher or lower dose. The highest maintenance dose of hydrocortisone MR that has been studied is 40mg. The lowest possible maintenance dosage should be used. In situations when the body is exposed to excessive physical and/or mental stress, patients may need additional substitution of hydrocortisone immediate release tablets especially in the afternoon/evening. See the Summary of Product Characteristics (SPC) for information on switching from conventional hydrocortisone therapy and also for details of treatment during intercurrent illness.

The 5mg and 20mg strengths contain the same excipients but, due to differences regarding the amount and the proportions of hypromellose, the strengths are not dose proportional.

Product availability date

October 2012
Hydrocortisone modified release tablet was designated an orphan medicine by the European Medicines Agency on 22 May 2006 for the treatment of AI.
Hydrocortisone modified-release tablets meet SMC orphan criteria.

Summary of evidence on comparative efficacy

Adrenal insufficiency (AI) is caused by failure of the adrenal cortex to produce cortisol and replacement glucocorticoid therapy is required (usually with hydrocortisone).[1] Hydrocortisone modified-release (MR) once daily formulation has been developed in an attempt to more closely reflect the physiological cortisol profile than the currently available hydrocortisone immediate-release (IR) formulation. Hydrocortisone MR is a dual release tablet. An outer coating allows initial rapid immediate drug release (within 10 minutes) followed by steady slower release from a gel matrix core over the first six to eight hours with the total dose being released and absorbed within 16 to 18 hours after dose intake.[1]

The main evidence is from a phase II/III randomised, controlled, open-label, 12-week crossover, bioavailability study that incorporated a 24-week uncontrolled extension study (DC 06/02).[2] Supportive data were provided by a subsequent five-year uncontrolled extension study plus two observational studies.[3,4,5]

Study DC 06/02 recruited 64 adult patients with primary AI (PAI), diagnosed more than six months previously, who were receiving a total daily dose of 20mg, 25mg, 30mg or 40mg oral hydrocortisone.[2] Patients had an initial four-week run-in phase in which those who had been receiving a twice daily regimen before the study were transferred to three times daily hydrocortisone IR at the same total daily dose. They were then randomised equally to receive open-label treatment for 12 weeks with once daily hydrocortisone MR or three times daily

hydrocortisone IR. On completion, they crossed over to receive 12 weeks of the alternative treatment at the same total daily dose of hydrocortisone (20mg to 40mg). Patients remained on their pre-study stable total daily dose of hydrocortisone throughout the study. However, in the event of an intercurrent illness, patients were instructed to double the daily dose of hydrocortisone. Patients taking once daily hydrocortisone MR were to take the additional dose eight (+/- two) hours after their normal morning dose. Following the randomised crossover phase, patients could receive hydrocortisone MR once daily (at the same dose as in the crossover phase) in a 24-week uncontrolled extension phase.[1,2] The aim of the study was to compare the bioavailability (area under the concentration-time curve [AUC]) of the two formulations and to determine if treatment with hydrocortisone MR reflects the diurnal profile of physiological serum cortisol.[1,2] Eighteen of the 64 patients underwent full single/multiple-dose standardised in-house pharmacokinetic sampling over 24 hours at randomisation and at the end of each 12-week period. The remaining 46 patients had fewer pharmacokinetic samples taken: single-dose sampling days 1 to 2 and multiple-dose sampling on days 7 to 8 in each crossover period.[2]

The primary outcome measured the difference between the two treatment regimens in multiple dose total serum cortisol over 24 hours (AUC 0 to 24 hours). It was analysed in the intention to treat (ITT) population which comprised all randomised patients with results from both crossover treatment arms.[1,2] The once daily hydrocortisone MR regimen resulted in a 19% lower mean total serum cortisol AUC 0 to 24 hours at multiple dosage than the three times daily hydrocortisone IR regimen, $p<0.0001$.[2]

Secondary outcomes included other bioavailability outcomes and clinical and biochemical parameters. Compared with the three times daily IR regimen, the once daily MR regimen resulted in a 6.4% higher serum cortisol AUC during the first four hours after the morning dose, a 30% lower AUC between 4 and 10 hours after the morning dose and a 59% lower AUC between 10 and 24 hours after the morning dose. Most (87%) patients receiving once daily hydrocortisone MR had one peak in serum cortisol concentration time profile compared with three peaks for all patients receiving IR hydrocortisone.[2]

After 12 weeks treatment with once daily hydrocortisone MR compared with three times daily hydrocortisone IR, outcomes that were significantly improved were: decrease in mean body weight (-0.7kg); decrease in mean systolic blood pressure (SBP -5.5mmHg) and in diastolic blood pressure (DBP -2.3mmHg); decrease in glycosylated haemoglobin (HbA1c) (-0.1%) and increase in mean concentration of the bone marker N-terminal propeptide of type I procollagen (PINP) (6.1µg/L). Outcomes that were significantly worsened were: increase in mean heart rate (2.2 beats/minute); decrease in mean serum high density lipoprotein cholesterol (-0.1mmol/L) and increase in serum triglycerides (0.2mmol/L). There was no difference between groups in fasting plasma glucose, insulin levels, total cholesterol, low density lipoprotein (LDL)-cholesterol, osteocalcin (bone marker), haematology parameters, electrolytes, liver function tests or thyroid stimulating hormone.[2]

Compliance with medication was calculated as a percentage of the tablets assumed to have been taken (quantity dispensed minus quantity returned) divided by the expected consumption (daily dose multiplied by the number of treatment days).[2] The result for each treatment group was over 100%.[1] This may be due to the requirement for increased doses for intercurrent illness; however, a robust comparison was not possible.

There was no evidence of a clinically significant improvement in health related quality of life (HRQoL) assessed using three validated methods with hydrocortisone MR over the IR formulation.[1] There was a statistically significant improvement after 12 weeks treatment with once

daily hydrocortisone MR compared with three times daily hydrocortisone IR in the psychosocial functioning subscale of the Fatigue Impact Scale (FIS) questionnaire and in the positive well-being subscale of the Psychological General Well-Being questionnaire (PGWB).[1] After 12 weeks of each treatment, significantly more study patients (85%) assessed their preference of once daily hydrocortisone MR, compared with three times daily hydrocortisone IR, as 'large' or 'very large'. The majority, 92% (59/64), of randomised patients elected to enter the six-month extension of DC 06/02.[2] There was no significant difference in tolerability between the treatments.[1]

Rescue therapy was required on a mean of 3.8% of days while taking once daily hydrocortisone MR compared with 1.9% of days while taking three times daily hydrocortisone IR. The increased requirement for hydrocortisone (as a proportion of the total dose during the 12 weeks period) in the respective treatment groups was 1.7% versus 1.1% due to intercurrent illness, and 0.4% versus 0.2% due to physical or mental stress.[2]

Study DC 08/01 was an uncontrolled, open-label five-year extension to DC 06/02 including 55 patients from the initial study plus an additional 16 patients with PAI who had not previously received hydrocortisone MR.[1,3] The dose of hydrocortisone MR could be adjusted at the discretion of the investigating clinician.[3] At the 18-month interim analysis, there was a statistically significant worsening in FIS total score from the baseline of study DC 08/01 (4.3 points) and also in the FIS psychosocial functioning variable (2.1 points). There were no statistically significant changes in the FIS variables from the DC 06/02 baseline.[1] PGWB scores were stable over time without any statistically significant changes from start of DC 08/01 or from baseline in DC 06/02 Part A to 18 months in DC 08/01. However, two patients withdrew due to impaired wellbeing.[1]

A non-randomised, open-label, single centre study has been conducted in patients with AI who had reduced HRQoL deemed to be at least partly due to non-physiological glucocorticoid replacement therapy.[4] Thirty out of 50 patients chose to change from their current conventional glucocorticoid treatment to once daily hydrocortisone MR. After a median follow-up of 128 days (hydrocortisone MR) and 338 days (conventional treatment), there were small but significant reductions in body mass index (BMI) and HbA1c with hydrocortisone MR compared with hydrocortisone IR. There was no significant difference in HRQoL.[4]

Results are available from an observational study conducted in 19 patients with PAI (Addison's disease). All patients switched from a total daily dose of 20mg hydrocortisone IR taken in three divided doses to 20mg hydrocortisone MR once daily. After one year, there was a significant improvement, compared with baseline, in waist circumference, HbA1c, total cholesterol and LDL–cholesterol levels. Cortisol peaks and AUC were similar. HRQoL was also statistically significantly improved compared with baseline.[5]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Safety data are limited because of the small number of patients (n=80) that have received hydrocortisone MR. The safety profile of the MR formulation is comparable to hydrocortisone IR although fatigue, gastrointestinal disorders and musculoskeletal disorders were reported more frequently during hydrocortisone MR once daily treatment, especially in the first eight weeks after switching from hydrocortisone IR three times daily.[1,2]

A total of 103 adverse events were reported in 73% (47/64) of patients receiving hydrocortisone MR once daily compared with 75 adverse events in 66% (42/64) of patients receiving hydrocortisone IR three times daily. The most common adverse events considered to be at least possibly related to study drug were fatigue (seven patients on once daily hydrocortisone MR versus two patients on three times daily hydrocortisone IR), nausea (three versus one) and vertigo (one versus two) in the respective groups.[1] There were eight serious adverse events (all infections), six during once daily treatment and two during three times daily treatment.[2]

Combined safety data for DC 06/02 and DC 08/01 at 27 months of follow-up for the 55 patients from the randomised crossover study and 18 months of follow-up for the 16 new patients have been published. A total of 19 patients reported 27 serious adverse events while receiving hydrocortisone MR once daily. Comparative rates of serious adverse events for hydrocortisone MR and IR formulations have been calculated though the duration of follow-up was longer for the MR formulation: 18.6 serious adverse events/100 patient years for hydrocortisone MR (up to 27 months follow-up) versus 13.3 serious adverse events/100 patient years for hydrocortisone IR (up to three months follow-up).[3]

As for other oral hydrocortisone products, the SPC for hydrocortisone MR provides recommendations for treatment during intercurrent illness. It also notes that lower cortisol exposure, which seems to be most evident in the afternoon, may be the cause of a worsening in wellbeing in patients switched to hydrocortisone MR from standard therapy. It notes: "In situations when the body is exposed to excessive physical and/or mental stress, patients may need additional substitution of immediate release hydrocortisone tablets especially in the afternoon/evening."[8]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

AI may be primary, due to disease in the adrenal glands (most commonly the autoimmune condition, Addison's disease) or secondary, due to impairment of the underlying hypothalamic-pituitary-adrenal axis.[1] Physiological cortisol levels increase in the early morning (between 2am and 4am), with maximum levels around 6am to 9am, and then decrease to low concentrations in the evening and very low concentrations around midnight.[1,9] Current standard replacement therapy is hydrocortisone IR, administered two or three times daily (usual total daily dose 15mg to 30mg). A higher dose (50% to 66% of the total daily dose) is taken in the morning on awakening. Prednisolone is an alternative replacement treatment.[9,10] Dexamethasone has also been used but is not recommended by the Endocrine Society because of the risk of Cushingoid side effects due to difficulties in dose titration.[10] Compared with healthy individuals, patients with AI who are receiving standard treatment have more cardiovascular risk factors (including abdominal obesity, hypertension and dyslipidaemia), and also have reduced HRQoL and bone mineral density. A potential reason is that the evening/night time plasma cortisol concentrations produced by standard hydrocortisone IR treatment are higher than normal physiological levels. The medicine under review is the first oral hydrocortisone MR product to be licensed and has been developed to more closely reflect the physiological diurnal serum cortisol profile.[1] Hydrocortisone MR meets SMC orphan criteria in view of European Medicines Agency (EMA) designation as an orphan medicine in this indication.

The pivotal study demonstrated that hydrocortisone MR tablets have approximately 20% lower bioavailability than hydrocortisone IR tablets, and that hydrocortisone MR produced a higher concentration of serum cortisol during the first four hours after the morning dose and lower concentrations in the late afternoon/evening.[1,2] Compared with the known physiological cortisol profile in healthy volunteers, hydrocortisone MR produced higher cortisol levels in the morning and lower levels in the afternoon and evening. Other differences from the physiological profile were the lack of a gradual increase up to the morning cortisol peak (normally starting at the third hour of sleep) and lack of the two daytime spikes (associated with eating, especially of high protein food).[1] The European Public Assessment Report (EPAR) states that it cannot be claimed that hydrocortisone MR has a physiological pharmacokinetic profile.[1] Some patients receiving hydrocortisone MR in the pivotal study felt worse in the afternoon compared with standard treatment. An EMA Scientific Advisory Group advised that there is little identifiable risk associated with potential hypocortisolism late in the day, and this is not of concern. The group highlighted that cortisol levels should be low in the evening to minimise the risk of short-term adverse effects such as insomnia as well as other long-term adverse effects such as cardiovascular complications and osteoporosis. There is a lack of robust data to support a claim of an improved metabolic profile and therefore of reduced cardiovascular risk. There is no study evidence that the once daily MR formulation improved patient compliance compared with standard treatment. There was no clinically significant improvement in HRQoL. [1]

The pivotal study had a number of limitations. It was of short duration, comprising only 12 weeks randomised treatment with each medicine. The company stated that blinding of study medication was not possible. The biochemical and safety outcomes were judged by the investigators to be unaffected by lack of blinding; however, tolerability and wellbeing results should be interpreted with caution.[1] The Committee for Medicinal Products for Human Use (CHMP) noted concerns about the pharmacokinetic analysis but concluded that it may be considered sufficiently reliable for the general pharmacokinetic characterisation of the formulation. However, there is uncertainty regarding the comparison with physiological levels due to unknown possible differences in the immunoassay used in publications describing the physiological concentration time profile and the immunoassay used in study DC 06/02.[1] The submitting company noted that the CHMP advised that only patients with PAI be included in order to improve the robustness of the study. All patients were Swedish and it is not known if there would be any relevant differences from the Scottish population with AI.[2] Most patients (78%) were receiving a total daily dose of at least 30mg hydrocortisone, which is higher than recommended by current guidance. The usual daily dose recommended by the National Institute for Health and Care Excellence (NICE) is 15mg to 30mg, and by the Endocrine Society is 15mg to 25mg.[10,11] No evidence has been presented comparing hydrocortisone MR with once daily prednisolone, which clinical experts consulted by the SMC advise may be used in patients who do not comply well with, or are intolerant of, standard hydrocortisone IR therapy.

Clinical experts consulted by SMC advised that a small number of patients have compliance issues or have adverse symptoms with current treatment and hydrocortisone MR may provide benefit in this patient group. However, improved compliance was not demonstrated in the clinical studies.

Summary of patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and a clinical specialist was held to consider the added value of hydrocortisone MR (Plenadren®), as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Adrenal insufficiency is a relatively rare condition which can be associated with a reduced quality of life. Studies also suggest an excess of mortality.

- Replacement of cortisol and aldosterone often restores well-being; however, some patients report persisting symptoms that impact on quality of life despite optimised standard replacement therapy.

- Under-replacement carries a risk of persisting adrenal insufficiency symptoms (such as fatigue, muscle weakness, weight loss and abdominal pain) and over-replacement increases the risk of glucocorticoid side effects (such as weight gain, diabetes and osteoporosis). Patients are at risk of life-threatening 'adrenal crisis' if they omit or fail to increase replacement in the context of acute illness.

- PACE participants advised that hydrocortisone MR offers the opportunity for improved symptom control and health-related quality of life in view of reports of fewer adrenal crises (and hospital admissions), balanced energy levels, stability of mood and an overall feeling of 'normality' and well-being compared to standard replacement therapy.

- For patients where the standard formulation is not an option then treatment with the MR formulation may allow individuals to continue an active independent life.

- Once daily administration has advantages in terms of compliance and may be of particular benefit in patients with co-morbidities and complex medication needs.

- The smoother pharmokinetic profile of hydrocortisone MR may offer a reduction in longer-term complications of cortisol replacement therapy.

Additional Patient and Carer Involvement
We received patient group submissions from Addison's Disease Self Help Group and The Pituitary Foundation. Addison's Disease Self Help Group has received 12.5% pharmaceutical company funding in the past two years, but none from the submitting company. The Pituitary Foundation has received 10.6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both patient groups also participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing once daily hydrocortisone MR to three times daily hydrocortisone IR for the treatment of adult patients with primary adrenal insufficiency. The time horizon used in the analysis was a lifetime horizon. SMC clinical experts have indicated that hydrocortisone IR is the comparator most likely to be displaced in Scotland. However, prednisolone was also mentioned by experts as a possible treatment option for patients with compliance issues, and this may be relevant as clinical experts highlighted that it is in this group of patients that hydrocortisone MR may have a role in practice.

A Markov (health state transition model) was submitted by the company. Patients entered the model receiving either MR or IR hydrocortisone treatment and progressed according to the risk of experiencing fractures, cardiovascular (CV) events, diabetes and diabetes-related complications. Within the model, the risk of death from CV events, fractures and diabetes, was used only to derive life years but these events did not influence quality of life.

The clinical data used in the economic analysis in relation to the impact on long term outcomes were derived primarily from study DC06/02; secondary outcomes from the clinical study were used to estimate the impact of treatment with hydrocortisone MR (versus IR) on long term events (e.g. mortality). These outcomes showed that hydrocortisone MR resulted in a significant difference in body weight (-0.7kg, p=0.005), SBP (-5.5mmHg, p=0.0001), HbA1c (-0.1%, p=0.0006) and PINP (increase of 6.1µg/L, p=0.004). The economic model used these results to inform the risk of developing long-term health outcomes ie risk of developing cardiovascular events, fractures and diabetes. These risks were estimated by applying a series risk equations from the UK Prospective Diabetes Study (UKPDS) and other published literature.

Quality of life was not calculated according to a standard economic modelling approach ie attaching utility values to individual health states within the model. Instead, the company used a simplifying assumption where HRQoL was determined only according to the treatment provided and the age of the patient. Patients therefore received a treatment-specific utility value for the duration of the model, but disutilities associated with disease-related longer term events were not accounted for. Within the model, age-specific utility values from the general UK population were adjusted according to the type of treatment received, which resulted in patients in the hydrocortisone MR arm having better HRQoL for the duration of the model time horizon. This was the key driver of the QALY gain with hydrocortisone MR. In order to estimate the treatment-specific utility values, baseline EQ-5D data from the UK general population were adjusted by applying data from a Swedish patient survey, in which patients with primary AI receiving either hydrocortisone MR or IR reported on HRQoL using the EQ-5D-5L.

In terms of medicine costs, in the base case analysis the company estimated the cost of hydrocortisone MR based on the mean number of hydrocortisone IR tablets per day (daily dose distribution) from the EU-Air registry. Additional costs included in the model were direct medical costs relating to cardiovascular events, hip fractures and diabetes. However, the key cost driver within the analysis was medicines costs. No adverse event costs were included.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price. SMC would wish to

present the with-PAS cost-effectiveness estimates that informed the SMC decision but is unable to publish these owing to the commercial confidentiality of the PAS. As such, only the without-PAS figures can be presented. Similarly, the estimated QALY gain associated with treatment is commercial in confidence and cannot be published. The base case results (without-PAS) indicated that hydrocortisone MR had an incremental cost per quality adjusted life year (QALY) of £26,140.

One-way and scenario analyses were provided by the company. In terms of the one-way analysis, results were most sensitive to a 20% decrease in the adrenal insufficiency relative utility adjustment factor and a 20% decrease in hydrocortisone MR utility (both of which reduced the HRQoL benefit assumed for the hydrocortisone MR arm). Based on these analyses, the incremental cost-effectiveness ratio (ICER) increased to £32,671 and £31,025 respectively without-PAS. For the scenario analyses presented, the ICER was most sensitive to the source used for hydrocortisone IR dosing assumptions. When the proportion of patients per strength was based on the pivotal study DC06/02, the ICER increased to £35,070 without-PAS. Assuming that the proportion of patients per strength was based on the DC08/01 extension study, the ICER increased to £34,303 without-PAS.

There were a number of weaknesses with the analysis, including;

- The model structure is unusual and results in the majority of the QALY gain being derived primarily from an assumption of improved HRQoL associated with hydrocortisone MR treatment. This quality of life gain is associated with significant uncertainty. The company based this assumption on EQ-5D data from an unpublished, company-sponsored study of Swedish patients with AI, which were then valued using the UK tariff. However, there is some uncertainty surrounding the applicability of these data within a Scottish population and this uncertainty is compounded by differences between the treatment arms. From the information provided by the company it is clear that the MR and IR groups differ in terms of patient characteristics, age, duration of treatment and patient numbers. Therefore it is likely that these may be the explanatory factors which result in different utility values observed for these groups. Given these issues, the company's assumption that improved HRQoL is solely due to patients feeling better on hydrocortisone MR is not supported by robust evidence. In addition, SF-36 data were available from the pivotal study (but not used in the base case economic analysis) and the results indicated that hydrocortisone MR did not result in a significant HRQoL improvement compared to hydrocortisone IR. When utility values derived from the SF-36 analysis were used in sensitivity analysis, the ICER rose to £99,847 without-PAS.
- There are considerable uncertainties surrounding the clinical data used in the economic analysis. The model assumes that changes in short-term study endpoints (PINP, BMI, SBP, and HbA1c) affect long-term outcomes ie risk of developing hip fractures, cardiovascular disease and diabetes. However, due to the lack of robust clinical data linking short-term study endpoints to longer term health outcomes, this assumption remains uncertain. The company has provided scenario analysis, whereby the impact of hydrocortisone MR tablets on all long-term outcomes has been removed. Based on this analysis, the without-PAS ICER increases to £31,895.
- As noted above, SMC experts have noted that hydrocortisone MR may be considered for patients where compliance is a concern. For this subgroup of patients, prednisolone may be considered to be a relevant comparator.

The Committee considered the benefits of hydrocortisone MR in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that

as hydrocortisone MR is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept hydrocortisone MR for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

In March 2016, the National Institute for Health and Care Excellence (NICE) last revised its Clinical Knowledge Summary of Addison's disease. The summary notes that: "*hydrocortisone is usually used for glucocorticoid replacement, but longer-acting glucocorticoids, such as prednisolone and dexamethasone, are sometimes used to avoid the peaks and troughs which may occur with hydrocortisone. The daily adult dosage of hydrocortisone is usually 15mg to 30mg in divided doses. Dosage depends on body weight, metabolism, and absorption. Ideally glucocorticoid replacement should resemble the natural cycle of corticosteroid release. Three divided doses are usually given (for example 10mg on waking, 5mg at noon, and 5mg in the early evening), as this aims to provide even levels of glucocorticoid throughout the day. Two divided doses are also an option (for example 15mg in the morning, and 10mg in the afternoon or early evening), but there is some opinion that this may lead to more variation in cortisol levels*."[11]

The Endocrine Society published a clinical practice guideline on Diagnosis and Treatment of PAI in 2016. This recommends glucocorticoid therapy in all patients with confirmed PAI and suggests using hydrocortisone (15mg to 25mg) or cortisone acetate (20mg to 35mg) in two or three divided oral doses per day. The recommendation specifies that the highest dose should be given on awakening in the morning, with the next either in the early afternoon (two hours after lunch if a two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be advantageous in individual patients. Prednisolone 3mg to 5mg daily is an alternative to hydrocortisone, especially in patients with reduced compliance. Dexamethasone is not recommended for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration.[10]

Additional information: comparators

Current standard treatment is hydrocortisone IR two or three times daily and there is also some use of prednisolone.[9]

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Hydrocortisone MR	**15mg to 30mg orally once daily**	**2,912 to 6,443**
Prednisolone	3mg to 5mg orally daily in one or two divided doses*	11 to 30
Hydrocortisone IR	15mg to 30mg orally daily in two or three divided doses	1,429 to 2,175

Doses are for general comparison and do not imply therapeutic equivalence. Cost of hydrocortisone products from eVadis on 01.11.16; cost of prednisolone from dm&d on 01.11.16. MR=modified release; IR=immediate release *dose from Endocrine Society Clinical Practice Guideline.[10]

Additional information: budget impact

The submitting company estimated there would be 2,195 patients eligible for treatment with hydrocortisone in year 1 and 2,550 patients in year 5, to which confidential estimates of treatment uptake were applied.

Without PAS

The gross impact on the medicines budget was estimated to be £137k in year 1, rising to £224k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £47k in year 1, rising to £78k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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2. Johannsson G, Nilsson AG, Bergthorsdottir R et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab 97: 473–481, 2012.

3. Nilsson AG, Marelli C, Fitts D et al. Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency. Eur J Endocrinol 2014 171(3):369-77.

4. Quinkler M, Nilsen RM, Zopf K et al. Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. European Journal of Endocrinology 2015 172, 619–626.

5. Giordano R, Guaraldi F, Marinazzo E et al. Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. Endocrine (2016) 51:360–368.

6. *Commercial In Confidence*.*

7. *Commercial in Confidence**

8. Hydrocortisone 5mg and 20mg modified-release tablets (Plenadren®). Summary of product characteristics. Shire Pharmaceuticals Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/. Last updated 09 June 2016.

9. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2015 3 (3):216-26.

10. Bornstein SR, Allolio B, Arlt W et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101(2):364-89.

11. National Institute for Health and Care Excellence. Clinical Knowledge Summaries: Addison's disease. 2014 http://cks.nice.org.uk/addisons-disease.

This assessment is based on data submitted by the applicant company up to and including 19 August 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG) established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.